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Profile of Fruquintinib in the Management of Advanced Refractory Metastatic Colorectal Cancer: Design, Development and Potential Place in Therapy

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Abstract: Colorectal cancer (CRC) is a prevalent and deadly cancer, with metastatic CRC (mCRC) often leading to poor outcomes despite advancements in screening and chemotherapy. Anti-angiogenic agents targeting vascular endothelial growth factor (VEGF) pathways have become essential in mCRC treatment. Bevacizumab, a VEGF inhibitor, was the first agent used in this context. However, drug resistance prompted the development of more selective inhibitors, such as fruquintinib, a tyrosine kinase inhibitor (TKI) that targets VEGFR-1, −2, and −3. Fruquintinib has shown promise in clinical trials, particularly for third-line mCRC treatment. The Phase III FRESCO trial in China demonstrated its efficacy, significantly improving overall survival (OS) and progression-free survival (PFS) compared to placebo, with manageable safety concerns like hypertension and hand-foot skin reactions. The FRESCO-2 trial extended these findings to European and North American populations, leading to a recent FDA approval for previously treated mCRC patients. The pharmacodynamic profile of fruquintinib includes potent inhibition of VEGFR, angiogenesis, and lymphangiogenesis. It has shown synergistic effects when combined with other treatments like chemotherapy and immune checkpoint inhibitors (ICIs). Current research focuses on exploring fruquintinib's combination with ICIs, such as PD-1 inhibitors, to enhance treatment efficacy, especially in microsatellite stable (MSS) CRC. Ongoing trials are investigating Fruquintinib's potential in combination with other therapies and its use in earlier lines of treatment. While promising, further studies are required to optimize its place in therapy and identify predictive biomarkers for better patient selection.

Keywords: fruquintinib, angiogenesis, VEGF inhibitor, refractory mCRC, third-line

Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer death, affecting almost 2 million people per annum.[1] Around half of CRC patients develop distant metastasis and the overall survival rate is 15% at 5 years.[2,3] Screening colonoscopy and stool occult blood testing have decreased mortality rates. However, treatment development is still suboptimal. Currently, the mainstay therapies are chemotherapy with agents like fluoropyrimidines, oxaliplatin and irinotecan.[4] Combining chemotherapy with monoclonal antibodies is the standard of care for microsatellite stable metastatic CRC (mCRC). These antibodies are drugs directed against either the epidermal growth factor receptor (EGFR) or the vascular endothelial growth factor (VEGF) based on the patient's molecular profile and the primary tumor location.[2,5] Unfortunately, most patients with mCRC eventually become nonresponsive, insensitive, or intolerant to these treatments, and the options are still limited for CRC patients who progress after 2 lines of treatment.[6] In this article, we will review the design, development, and potential place of fruquintinib, a new oral VEGFR inhibitor for third- or later-line use in mCRC patients.

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Blockage of Vascular Endothelial Growth Factor Receptor (VEGFR)

Angiogenesis is the generation of new blood vessels from existing vasculature, it plays a role in embryonic development and tumorigenesis.[7,8] It is a main element in cell proliferation, vascular remodeling, and cancer metastasis. The VEGF is a crucial pathway of angiogenesis.[9] The blockage of angiogenesis has become an effective treatment for multiple cancer types.[10] Anti-angiogenic agents function by blocking the ligand (VEGF inhibitors) or the receptor (VEGFR inhibitors).

Bevacizumab is a humanized monoclonal antibody against the VEGF-A ligand, it is the first drug that achieved approval in combination with chemotherapy for mCRC.[8] It functions by binding to VEGF, thus, preventing it from binding to its receptor. Therefore, jeopardizing the signal transduction pathway that leads to angiogenesis, proliferation, and migration of cancer cells.[11] Later in a pivotal trial, Bevacizumab was discovered to work in second-line settings or for patients with disease progression.[12] Blocking VEGF-A leads to an increase in other components in the VEGF axis such as VEGF-C, VEGF-D, and the platelet-derived growth factor (PDGF), eventually leading to resistance to bevacizumab treatment. This was confirmed by Hayashi et al during their evaluation of serum concentrations of biomarkers before and after treatment with a combination of bevacizumab and the FOLFIRI regimen (folinic acid, fluorouracil, and irinotecan). They have found decreased VEGF-A levels, but higher levels of VEGF-C and VEGF-D compared to baseline both in bevacizumab-pretreated and bevacizumab-naïve patients.[13] This poor target selectivity that might lead to off-target toxicities has led to the development of other drugs that target multiple VEGF ligands simultaneously. Other limitations to the clinical use of bevacizumab were the intravenous dosing, autoimmune disease following long-term treatment, immunogenicity, and high cost. Thus, there was a need for a new active small molecule orally-given VEGFR inhibitor that can be combined with chemotherapy.[14]

Thus, fruquintinib, a highly selective tyrosine kinase inhibitor (TKI) of VEGFR-1, −2, and −3 was approved in China, in 2018, for third- or later-line in the treatment of mCRC according to the phase III FRESCO trial on Chinese patients.[15,16]

Pharmacodynamic and Pharmacokinetic Characteristics of Fruquintinib

The chemical reaction that led to the synthesis of fruquintinib was first reported in 2009, with the C-O coupling between 4-chloro-6,7-dimethoxyquinazoline and 6-hydroxy-N,2-dimethylbenzofuran-3-carboxamide, yielding to the agent 6-[6,7-dimethoxyquinazolin-4-yloxy]-N, 2-dimethylbenzofuran-3-carboxamide, known as fruquintinib with an 85% high yield (Figure 1).[17]

Fruquintinib (HMPL-13) achieved inhibition of VEGFR-1, −2, and −3 with IC50 values at nanomolar levels (33, 35, and 0.5 nm, respectively) using in vitro biochemical kinase assays with recombinant human VEGFR enzymes.[18] It demonstrated significant anti-tumor efficacy in vivo, showing dose-dependent tumor growth inhibition in human tumor xenograft models, including colon cancer (HT-29, HCT-116), lung cancer (NCI-H460), and gastric cancer (BGC-823) cell lines.[18] It also demonstrated synergistic effects when combined with chemotherapy agents. In vivo, an 85%

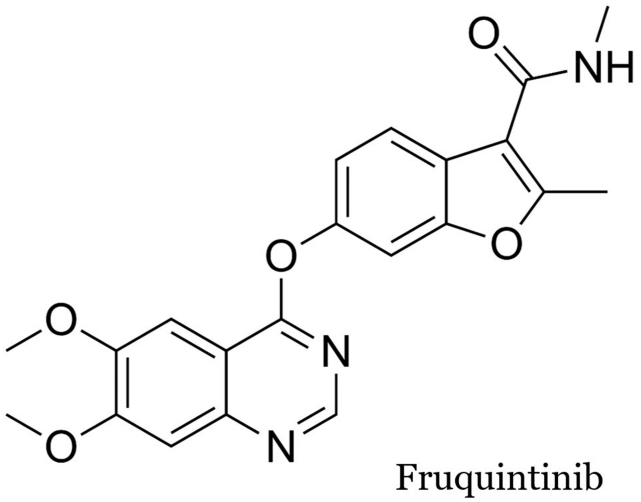

Figure 1 Chemical structure of fruquintinib. Reprinted from Wikipedia. Available from: https://en.wikipedia.org/wiki/Fruquintinib. Creative Commons.

inhibition of the VEGFR2 was achieved for 8 hours and more after a single dose of fruquintinib at 2.5 mg/kg in the lung tissue. As for the pharmacokinetic aspect, the corresponding plasma concentration was 176 ng/mL, which was the effective concentration of fruquintinib to achieve 85% target inhibition (EC85). The EC85 is beneficial to calculate the duration of target inhibition at the recommended doses in clinical trials.[18] Another study showed synergism in a murine tumor model when co-administering fruquintinib with targeted therapies like EGFR TKIs (gefitinib and theliatinib) and the c-MET inhibitor savolitinib, and also with an anti-PD-L1 inhibitor compared to fruquintinib alone.[19]

When fruquintinib binds with VEGFR, it causes a conformational change and dimerization, leading to phosphorylation of the intracellular kinase domain, and triggering signaling cascades including the PI3K/AKT, PKC, RAF/RAS, and ERK pathways (Figure 2).[20–22] VEGFR2 is critical in pro-angiogenic processes, as for VEGFR3, it is only expressed on lymphatic vessels and involved in lymphangiogenesis and metastasis of lymph nodes. The importance of lymphangiogenesis in cancer metastasis makes targeting VEGFR3 an attractive approach. There have been no products developed

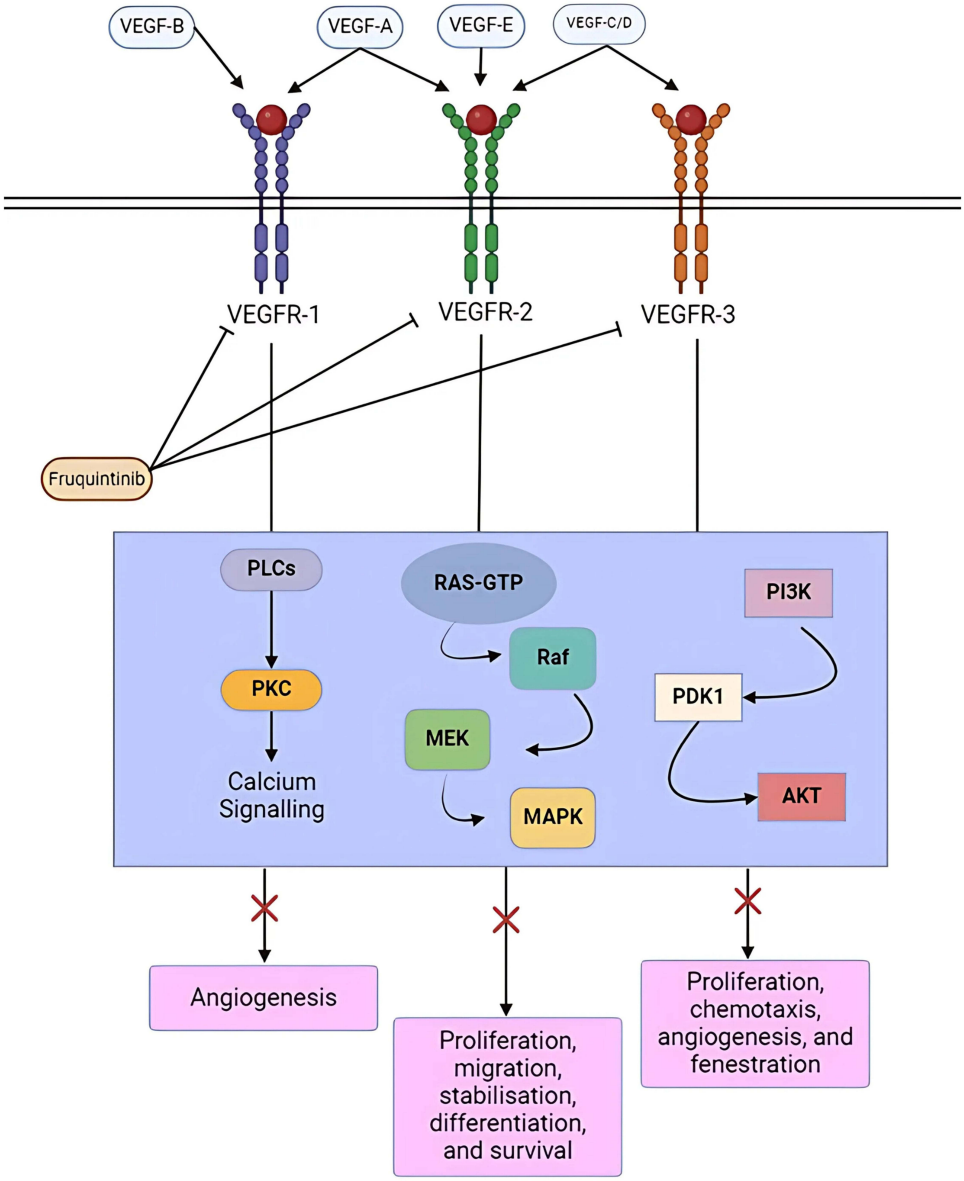

Figure 2 Blockage of VEGF receptors by fruquintinib and the affected signaling pathways. Created in BioRender. Nidal, A. (2025) https://BioRender.com/j82d874.
Abbreviations: VEGF, Vascular Endothelial Growth Factor; VEGFR, Vascular Endothelial Growth Factor Receptor; PLC, Phospholipase C; PKC, Protein Kinase C; RAS-GTP, Rat Sarcoma Protein bound to Guanosine Triphosphate; RAF, Rapidly Accelerated Fibrosarcoma; MEK, Mitogen-Activated Protein Kinase Kinase; MAPK, Mitogen-Activated Protein Kinase; PI3K, Phosphoinositide 3-Kinase; PDK1, Phosphoinositide-Dependent Kinase 1; AKT, Protein Kinase B.

particularly to target VEGFR3 before. However, fruquintinib targets both VEGFR2 and VEFR3, it could achieve an advantage by simultaneously halting both angiogenesis and lymphangiogenesis compared to drugs targeting VEGFR2 alone.[18]

Fruquintinib also showed a suppression effect on microvessel tube formation, which is essential in angiogenesis. At concentrations like 0.03 and 0.3 μmol/L, fruquintinib caused 74% and 94% shrinkage of the tubule length of human umbilical vein endothelial cells, respectively. Comparing to a parallel cell survival assay showed that this shrinkage was not due to cytotoxicity but rather due to VEGF/VEGFR inhibition.[18]

Clinical Development of Fruquintinib

In 2016, Cao et al published a Phase I trial that investigated the safety and pharmacokinetics of fruquintinib. The study included 40 Chinese patients diagnosed with advanced solid tumors including CRC, breast cancer, and NSCLC. Most of them were pre-heavily treated with 3 or more systemic treatments. The patients were grouped according to dosing regimens as either continuous or 3-week-on and 1-week-off. The maximum tolerated dose (MTD) was determined by monitoring dose-limiting toxicities (DLTs). DLTs were defined as grade 4 hematologic toxicity, grade 3 neutropenia with fever, grade 3 thrombocytopenia with bleeding, any grade 3 or above non-hematologic toxicity, or toxicities of any grade that resulted in the interruption of treatment for more than 2 weeks. The grading was according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.3. At 6-mg, two patients experienced DLTs, and the dose escalation was halted. For the continuous regimen, 4mg was recommended as the daily dose. The alternative 3-week-on/1-week-off regimen was suggested due to the long half-life of 42 hours. The 5-mg once daily was recommended for this regimen. Although the 6-mg dosing regimen was tolerated, the MTD was not determined. This regimen was suggested to reduce toxicities, as there was a clear trend between toxicities and drug exposure time. Systemic exposure to the drug was consistent in terms of different tumor types, and the pharmacokinetic characteristics were excellent.[23] A comparison study was published for these two regimens, and the 3-week-on/1-week-off regimen was recommended for the Phase II trial (RP2D).[24] All patients experience at least one adverse event (AE), including hand-foot skin reaction (HFSR), increased thyroid-stimulating hormone (TSH), proteinuria, hypertension, leukopenia, hoarseness, and others. As for grade 3/4 AEs, the most frequent were HFSR (17.5%) and hypertension (17.5%). As for the tumor response, according to the Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST v1.0) the disease control rate was 82.3%, partial response (PR) was found in 41.1%, and stable disease (SD) in 41.2% of patients.[23]

In the following year, Xu et al published a phase Ib expansion trial and a phase II randomized double-blinded study.[25] In phase Ib, fruquintinib was administered as a third-line treatment to 42 mCRC patients as a 3-week-on/1-week-off regimen. The median progression-free survival (PFS) was 5.8 (95% CI 4.01–7.60) months, and the median overall survival (OS) was 8.88 (95% CI 7.53–15.53) months. The objective response rate (ORR) was 9.5% (PR). Two-thirds of patients had SD for at least 8 weeks. The disease control rate (DCR) was 76.2%. The most common grade ≥3 AEs were hypertension (21.4%), HFSR (9.5%), and diarrhea (9.5%). Over 11.9% (n = 5) of patients discontinued treatment due to AEs. One death was reported due to lung metastasis but was considered treatment-related by the investigator. Thrombocytopenia, HFSR, and hypertension were the most common AEs that needed interruption of treatment or dose reduction.[25]

Phase II involved 71 mCRC patients who were randomized to receive either fruquintinib with best supportive care (n = 47) or placebo with best supportive care (n = 24). The PFS for the fruquintinib group was significantly higher than the placebo group (median PFS = 4.73 versus 0.99 months) with a hazard ratio (HR) of 0.30 (95% CI: 0.15 to 0.59). The median OS was 7.72 versus 5.52 months (HR = 0.71, 95% CI: 0.38 to 1.34). Hypertension and HFSR were the most common treatment-related AEs.[25]

The benefits in OS were comparable to the CONCUR trial, and the safety profile was comparable to CONCUR and CORRECT trials, both of which investigated regorafenib in previously treated Asian and global mCRC patients, respectively.[26,27]

After achieving efficacious results and an acceptable safety profile for fruquintinib. The FRESCO trial (Fruquintinib Efficacy and Safety in 3+ Line Colorectal Cancer Patients) in China involved 416 mCRC patients, of which, 278 patients received fruquintinib 5-mg orally once a day, following the 3-week-on/1-week-off regimen, and 138 patients received placebo. All patients were pretreated, and 30% had received prior VEGF inhibitor therapy. Significant prolongation of the OS was found (median OS: 9.3 versus 6.6 months), with an HR of 0.65 (95% CI: 0.51 to 0.83), as well as the PFS (median FPS: 3.7 versus 1.8

months), with an HR of 0.26 (95% CI: 0.21 to 0.34). Fruquintinib also showed higher ORR (4.7% versus 0%, p-value = 0.01) and DCR (62.2% versus 12.3%, p < 0.001). One patient from the fruquintinib group (0.4%) achieved a complete response.[15]

As for safety, 98.6% and 88.3% of patients had at least one treatment-emergent AE from the fruquintinib and the placebo groups, respectively. Grade ≥3 AEs were experienced by 61.2% and 19.7% of patients, respectively. Most of which were hypertension (21.2%), HSFR (10.8%), and proteinuria (3.2%). Less than 1.5% of patients in both groups experienced grade 3 hepatotoxicity.[15]

In China, treating patients with VEGF inhibitors is not routinely followed in first- or second-line therapy. Thus, the results provided by FRESCO were not generalizable to patients from North America and Europe. This led to the approval of fruquintinib in China in September 2017. Also, regorafenib and trifluridine-tipiracil were not yet approved.[28] Other trials are investigating fruquintinib in the treatment of advanced NSCLC (FALUCA trial: NCT02691299) and advanced gastric cancer (FRUTIGA trial; NCT03223376).[16]

The FRESCO-2 trial was carried out for patients who are treated in Europe and North America, which involved 124 hospitals across 14 countries. With similar allocation and treatment grouping as FRESCO, FRESCO-2 showed an improvement in OS (median: 7.4 versus 4.8 months, HR = 0.66, 95% CI: 0.55 o 0.80), PFS (median: 3.7 versus 1.8 months, HR = 0.32, 95% CI: 0.27 to 0.39), and similar rate of grade ≥3 AEs (hypertension in 14%, asthenia in 8%, and HFSR in 6% of patients). However, there was one treatment-related death in each treatment group. The DCR was 56% and 16% for the fruquintinib and the placebo groups (p < 0.0001), respectively. As for the ORR, the treatment difference was 2% and was not statistically significant (p = 0.059). Over 73% of these patients had received 3 or more previous lines of therapy. The efficacy of fruquintinib regardless of previous exposure to regorafenib could be explained by its higher target selectivity compared with other anti-VEGF/anti-VEGFR therapies.

After the evaluation of fruquintinib in the FRESCO and FRESCO-2 trials, the FDA approved fruquintinib on November 8, 2023, for adult mCRC patients who had received prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type and medically appropriate, an anti-EGFR therapy.[29,30]

Future Directions and Potential Place in Therapy

The development of a new antiangiogenic TKI such as fruquintinib is welcomed and solves a substantial problem regarding drug resistance during mCRC treatment. Immunotherapy modalities such as the anti-programmed death 1 (PD-1) inhibitors are recommended by the National Cancer Comprehensive Network (NCCN) and approved by the FDA for the treatment of microsatellite instability (MSI) mCRC. Marked improvements in PFS and ORR have been shown when using immune checkpoint inhibitors (ICIs) such as nivolumab and pembrolizumab. Thus, a strategy to treat high-MSI mCRC patients could be achieved by combining fruquintinib with a PD-1 inhibitor.[31]

A murine model study experimented with combining fruquintinib with anti-PD-1 for microsatellite stable (MSS) CRC. This combination decreased angiogenesis, enhanced the normalization of the vascular structure, and reduced tumor hypoxia. It also showed promising effects in the immune tumor microenvironment by enhancing chemotactic factor release, increasing CD8 + T cell infiltration and activation, decreasing the ratio of regulatory T cells, and promoting the M1/M2 ratio of macrophage.[32]

A Chinese retrospective study of 45 refractory mCRC patients who progressed to conventional chemotherapy with or without bevacizumab or cetuximab. They have found an ORR of 11.1%, a median PFS of 3.8 months, and a median OS of 14.9 months. Grade 3 AEs were experienced by 6.7% of patients. The PFS was comparable to previous studies that administered fruquintinib monotherapy, however, the ORR and OS were notably improved. Still, these results had to be confirmed by clinical trials.[33]

In March 2023, an open-label phase 1b/2 trial of fruquintinib combined with sintilimab for the treatment of advanced solid tumors was published. Forty-four mCRC patients were enrolled and an ORR of 23.8% was reported. As for survival, the PFS was 6.9 months, and the OS was 14.8 months. Grade ≥3 AEs were in 36.4% of patients in the 5-mg fruquintinib 2-week-on/1-week-off regimen group and 59.1% of patients in the 3-mg continuous group. The occurrence of hypertension (21.2%), HFSR (10.8%), and proteinuria (3.2%) was comparable to the FRESCO-2 trial, and it was suggested that combination therapy with sintilimab did not lead to overlapping toxicities. Although it should be noted with caution, this cross-trial comparison could pivot the way for

a new combinational modality for mCRC refractory patients.[34] The RP2D was determined as fruquintinib 5-mg 2w/1w combined with sintilimab 200 mg once every 3 weeks.

To date, ICIs have been effective only in a contingent of patients who are mismatch repair-deficient (dMMR) or MSI-H. The AtezoTRIBE phase II trial has shown promising results when combining an antiangiogenic agent like bevacizumab with atezolizumab, an ICI.[35] The REGONIVO phase Ib trial has also reported an ORR of 36% when combining regorafenib with nivolumab in mCRC patients.[36]

Other ongoing clinical trials are investigating the efficacy and safety of fruquintinib in combinational modalities with immunotherapy and even radiotherapy (NCT06099314, NCT06011330, NCT05747716). Also, the administration of fruquintinib in first-line settings is being investigated. A phase II trial (NCT05634590) and another single-center phase Ib/II trial (NCT05522738) are studying fruquintinib as a combination with chemotherapy in RAS-mutant mCRC. The optimal sequence of late-line therapies is also warranted for further research.[37]

A meta-analysis of 5 phase III trials has indirectly compared the efficacy of regorafenib, TAS-102, and fruquintinib and discovered similar OS between these agents but superior PFS for fruquintinib compared with TAS-102. Indirect comparison of grade ≥3 AEs showed lower rates of hypertension and proteinuria and higher rates of HFSR in regorafenib compared to fruquintinib.[38]

There is a gap in knowledge regarding predictive biomarkers in fruquintinib therapy. Factors that are potentially associated with treatment response in anti-VEGF/anti-VEGFR therapy include LDH, hERG1/aHIF-2α, and circulating angiopoietin-2.[37] A post-hoc analysis of the FRESCO trial showed that patients who experienced HFSR showed improved OS and PFS compared to others who did not experience HFSR.[39]

Conclusion

In conclusion, fruquintinib represents a significant advancement in the treatment of metastatic colorectal cancer (mCRC), particularly for patients who have exhausted other lines of therapy. Its high selectivity for VEGFR-1, −2, and −3 provides targeted inhibition of angiogenesis and lymphangiogenesis, offering a new avenue for disease control. Clinical trials, including FRESCO and FRESCO-2, have demonstrated improvements in both PFS and OS compared to placebo, establishing fruquintinib as an effective third-line or later treatment option. Additionally, its favorable safety profile, despite common adverse events like hypertension and HFSR, renders it a viable alternative to existing therapies.

The oral administration and manageable toxicity profile of fruquintinib are practical benefits for patients, especially when considering long-term treatment. Moreover, the drug's potential for synergy with immunotherapies, such as anti-PD-1 agents, suggests an exciting area for future exploration, particularly for microsatellite stable (MSS) mCRC patients, who have limited treatment options. Early preclinical and clinical studies supporting these combinations could expand the therapeutic reach and offer enhanced outcomes in mCRC treatment.

Overall, fruquintinib has introduced a new dimension to mCRC management, addressing a critical need for effective therapies in later-stage disease, and holds promise for further therapeutic developments in combination treatments.

Disclosure

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